REMARKS

The claims were previously amended in the response filed with the Request for Continued Examination (RCE) on February 1, 2005.

The Examiner rejected, in the final office action mailed on January 2, 2004, claims 43-46 under 35 U.S.C. § 112, ¶ 1 for lack of enablement with respect to vitamin receptors that are not the folate receptor. Claims 43-46 have been amended to specify ligands that bind to the folate receptor. Withdrawal of the rejection of claims 43-46 under 35 U.S.C. § 112, ¶ 1 is respectfully requested.

The Examiner rejected pending claims 1, 8-10, 13, 16, 18-38, 41-46, and 48-52 under 35 U.S.C. § 112, ¶ 1 in the final office action mailed on January 2, 2004 for lack of an adequate written description of the phrase "wherein said immunogen is not an antibody." Claims 16, 48-49, and 52 have been cancelled. Claims 1, 38, and 41-43, and their dependent claims, were amended to delete the phrase "wherein the immunogen is not an antibody" in the response filed with the RCE on February 1, 2005. Withdrawal of the rejection of claims 1, 8-10, 13, 18-38, 41-46, and 50-51 under 35 U.S.C. § 112, ¶ 1 is respectfully requested.

The Examiner rejected claims 16, 52, and 53 under 35 U.S.C. § 112, ¶ 1 in the final office action mailed on January 2, 2004. Claims 16 and 52 have been cancelled. Support for claim 53 is found, for example, on page 12, line 28 of the specification. Withdrawal of the rejection of claim 53 under 35 U.S.C. § 112, ¶ 1 is respectfully requested.

The Examiner rejected pending claims 1, 8-10, 13, 16, 18-38, 41-46, and 48-52 under 35 U.S.C. § 112, ¶ 1 in the final office action mailed on January 2, 2004. In the Examiner's Advisory Action, mailed on June 25, 2004, the Examiner stated that "[t]he cancellation of the limitation "wherein said immunogen is not an antibody" would overcome the rejection under 112, ¶ 1 for new matter, but would result in the re-applying of the 102(b) rejection as being anticipated by Roy et al." Claims 16, 48-49, and 52 have been cancelled. Claims 1, 8-10, 13, 18-38, 41-46, and 50-51 were amended to delete the phrase "wherein the

immunogen is not an antibody" in the response filed with the RCE on February 1, 2005 as discussed above.

In the office action mailed on March 21, 2003 (the office action prior to the final office action), the Examiner rejected claims 1-8, 13, 26, 36, 43, and 47 under 35 U.S.C. § 102(b) over Roy et al. Claims 1, 8, 13, 26, 36, and 43 remain pending. Roy et al. discloses a method of targeting tumor cells using a ligand-Fv fragment conjugate where the Fv fragment is a small, single-chain antibody fragment directed to the T-cell receptor. The Fv fragment binds T cells and localizes T cells to the site of the tumor. As stated on page 13, line 24 of the March 21, 2003 office action, the Examiner's rejection was based on the argument that the anti-T cell receptor antibody disclosed in Roy et al. is an immunogen.

Applicants traversed the Examiner's argument in the response filed with the RCE on February 1, 2005, but Applicants reiterate their arguments in this response. If the small, single-chain Fv fragment disclosed in Roy et al. was an immunogen, the method disclosed in Roy et al. would be inoperable. The single-chain Fv fragment in the ligand-Fv fragment conjugate disclosed in Roy et al. must bind T cells to localize T cells to the site of the tumor for the method disclosed in Roy et al. to be operable. If the Fv fragment was an immunogen, antibodies directed to the Fv fragment would bind to that fragment and block T cell binding. Thus, the basis for the Examiner's rejection in the March 21, 2003 office action would result in the method disclosed in Roy et al. being inoperable. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 8, 13, 26, 36, and 43 over Roy et al.

The Examiner also rejected pending claims 43, 45, 46, and 50-51 under 35 U.S.C. § 103(a) in the final office action mailed on January 2, 2004 over Cowan in combination with various secondary references. Cowan was published on May 10, 2001 and the 102(e) date for Cowan is January 19, 2000. The captioned application was filed on March 30, 2001 and claims priority to Provisional Application Serial No. 60/193,944, filed

on March 31, 2000, and to Provisional Application Serial No. 60/255,846, filed on December 15, 2000. Submitted herewith is the Declaration under 37 C.F.R. § 1.131 of Dr. Philip S. Low establishing that the claimed invention was conceived and reduced to practice prior to January 19, 2000. Accordingly, Cowan is not prior art to the claimed invention, and withdrawal of the rejection of claims 43, 45, 46, and 50-51 over Cowan in combination with the cited secondary references is respectfully requested.

The Examiner has also rejected pending claims 1, 8-10, 13, 18-35, 38, 41-43, 45-46, 48-52, and 54 over Pouletty in combination with various secondary references under 35 U.S.C. § 103(a) in the final office action mailed on January 2, 2004. Claims 48-49 and 52 have been cancelled. As discussed in previous responses, Applicants contend that *prima facie* obviousness has not been established. However, as discussed in the interview with the Examiner, even if the Examiner has established a *prima facie* case of obviousness, the Examiner's § 103 rejection has been overcome based on unexpected results (*i.e.*, the unexpected synergism and the unexpected complete disappearance of tumors) obtained with Applicants' claimed methods and compositions for use in targeting and destroying cancer cells.

As the court concluded in *In re Diamond*, the question of nonobviousness must turn on whether the *prima facie* case of obviousness of the claimed composition is rebutted by a showing of unexpected results. *In re Diamond*, 53 CCPA 1172, 360 F.2d 214, 149 USPQ 562 (1966). *In re Meinhardt*, 55 CCPA 1000, 392 F.2d 273, 157 USPQ 270 (1968). Synergism is an example of an unexpected result. The courts have defined synergism as an effect where the "whole in some way exceeds the sum of its parts," or when the combination produces a "new or different function," or "unusual or surprising consequences." *Philips Industries Inc. & Mobil Temp. Inc. v. State Stove & Manufacturing Co., Inc.*, 522 F. 2d 1137 (6th Cir. 1975). Furthermore, as stated in MPEP § 716.02(a), "[e]vidence of a greater than expected result may also be shown by demonstrating an effect

which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)." Thus, a synergistic effect is an effect which is greater than the sum of the effects of the individual components of a composition.

As shown by the Declaration under 37 C.F.R. § 1.132 of Dr. Barton A. Kamen submitted herewith, and as shown by the results discussed in Examples 7 (see Fig. 7) and 16 (see Fig. 16) in the captioned application, strong synergism is obtained with Applicants' claimed invention. As shown by the data in Fig. 1 in the Declaration and the data in Figs. 7 and 16 in the captioned application, a strong synergistic effect is obtained with the combination of ligand-immunogen conjugates and cytokines compared to the greatly reduced effects obtained with ligand-immunogen conjugates or cytokines alone. The synergistic increase in median survival times for mice treated with ligand-immunogen conjugates in combination with cytokines is an effect which is much greater than the sum of each of the individual effects taken separately. Accordingly, a strong synergistic effect is obtained with Applicants' claimed methods and compositions. See MPEP § 716.02(a).

The method described and claimed in the present application is now in Phase I clinical trials as a cancer therapy, and, in assays performed by the inventors and by employees of the licensee, for submission to the FDA in Investigational New Drug Study Reports, complete disappearance of tumors in up to 100% of mice with no observed recurrence of disease has been obtained, and this complete disappearance of tumors is consistently obtained (see the Declaration under 37 C.F.R. § 1.132 of Dr. Barton A. Kamen). The ligand-immunogen conjugates or cytokines alone each have considerably reduced effects with the maximum response observed with the ligand-immunogen conjugates or the cytokines alone being 37.5% and 25%, respectively. Accordingly, an unexpected complete disappearance of solid tumors in up to 100% of mice is observed with Applicants' claimed methods and compositions.

The Federal Circuit in *In re Dillon* concluded that a *prima facie* case of obviousness can be rebutted by "showing that the claimed compositions possess *unexpectedly improved properties or properties that the prior art does not have.*" *In re Dillon*, 919 F.2d 688, 692, 16 U.S.P.Q. 2d 1897, 1901 (Fed. Cir. 1990). (emphasis added). The prior art does not have the properties of Applicants' claimed methods and compositions because the ligand-immunogen conjugates of Pouletty were never combined with the cytokines described in Smith and Insel. Furthermore, none of the cited references makes any mention of any synergistic effect, or any mention of complete disappearance of tumors, with the combination of ligand-immunogen conjugates and cytokines as is obtained with Applicants' claimed invention. Thus, the strong synergism and the complete disappearance of tumors in up to 100% of mice obtained with the presently claimed methods and compositions are properties that the cited prior art does not have and are unexpectedly improved properties. Clearly, the strong synergism and the complete disappearance of tumors in up to 100% of mice obtained with Applicants' claimed invention are unexpected results, particularly when no such effects were reported in the prior art. Accordingly, even if the Examiner has made a *prima facie* case of obviousness, and Applicants contend that the Examiner has not, the Applicants have rebutted the Examiner's *prima facie* case by demonstrating that Applicants' claimed methods and compositions have unexpectedly improved properties that the prior art does not have.

Accordingly, it could not have been obvious at the time the invention was made that ligand-immunogen conjugates would act synergistically with cytokines in causing the potent stimulation of the endogenous immune response that results from Applicants' claimed methods and compositions, or that complete disappearance of tumors could be obtained with Applicants' claimed invention. In particular, the strong synergism and complete disappearance of tumors that has been demonstrated using Applicants' claimed methods and compositions was clearly an unexpected result because 1.) there was no description in the prior art at the time the invention was made of the use of any ligand-

immunogen conjugate in combination with any cytokine, and 2.) there was no suggestion in the prior art of the potent synergistic effect observed with Applicants' claimed methods and compositions or of the complete disappearance of tumors in up to 100% of mice that can be obtained with Applicants' claimed invention. Clearly, the large synergistic effect and the complete disappearance of tumors obtained using Applicants' claimed methods is an unexpected result when compared to the results achieved by the prior art since no results were achieved in the prior art. Withdrawal of the rejection of claims 1, 8-10, 13, 18-35, 38, 41-43, 45-46, 50-51, and 54 under 35 U.S.C. § 103(a) over Pouletty in view of the cited secondary references is respectfully requested.

CONCLUSION

The foregoing amendments and remarks are believed to place the claims in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance.

Respectfully submitted,

Rebecca Ball

Rebecca L. Ball
Registration No. 46,535
Attorney for Applicants

RVB:wlb
(317) 231-7511
Indianapolis, Indiana 46204

APPENDIX (Pending Claims)

1. (Previously presented) A method of enhancing an endogenous immune response-mediated specific elimination of a population of cancer cells in a host animal harboring said population wherein the members of said cell population have an accessible binding site for a folate receptor-binding ligand, said method comprising the step of

administering to said host a composition comprising an immunogen conjugated to a folate receptor-binding ligand selected from the group consisting of folate and analogs and derivatives thereof wherein the immunogen is recognized by an endogenous or an exogenous antibody in the host or is recognized directly by an immune cell in the host; and

administering to said host a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the conjugate.

2. (Canceled)

3. (Canceled)

4. (Withdrawn) The method of claim 1 wherein the population of pathogenic cells is an exogenous pathogen or an endogenous cell population harboring exogenous pathogens.

5. (Withdrawn) The method of claim 4 wherein the exogenous pathogen is selected from the group consisting of bacteria, fungi, viruses, mycoplasma, and parasites.

6. (Canceled)

7. (Canceled)

8. (Previously presented) The method of claim 1 wherein the folate receptor-binding ligand is chemically complexed to the immunogen through bonding selected from the group consisting of covalent, ionic, and hydrogen bonding.

9. (Previously presented) The method of claim 8 wherein the folate receptor-binding ligand is a folic acid analog having a glutamyl moiety covalently linked to the immunogen only via the glutamyl γ-carboxyl moiety of the ligand.

10. (Previously presented) The method of claim 8 wherein the folate receptor-binding ligand is a folic acid analog having a glutamyl moiety covalently linked to the immunogen only via the glutamyl α-carboxyl moiety of the ligand.

11. (Canceled)

12. (Canceled)

13. (Previously presented) The method of claim 1 wherein the ligand is an organic molecule capable of binding to a receptor and wherein said receptor is preferentially expressed, uniquely expressed or overexpressed on the surface of said population of cancer cells.

14. (Withdrawn) The method of claim 12 wherein the small organic molecule is an antimicrobial drug.

15. (Withdrawn) The method of claim 1 wherein the ligand is a ß-lactam antibiotic.

16. (Cancelled)

17. (Canceled)

18. (Original) The method of claim 1 wherein the immunogen is an organic molecule having a molecular weight less than 20,000 daltons.

19. (Previously presented) The method of claim 18 wherein the organic molecule is fluorescein or dinitrophenyl.

20. (Original) The method of claim 1 wherein the immunogen is an α-galactosyl group.

21. (Original) The method of claim 1 wherein the antibody is exogenous to said host and is co-administered with said conjugate composition.

22. (Previously presented) The method of claim 1 wherein the compound capable of stimulating an endogenous immune response comprises a cytokine.

23. (Previously presented) The method of claim 22 wherein the cytokine comprises IL-2, IL-12, IL-15, or combinations thereof.

24. (Previously presented) The method of claim 22 wherein the cytokine comprises IL-2, IL-12, IL-15, or combinations thereof, in combination with IFN-α or IFN-γ.

25. (Previously presented) The method of claim 22 wherein the cytokine comprises IL-2, IL-12, IL-15, or combinations thereof, in combination with IFN-α or IFN-γ, or a combination thereof, and GM-CSF.

26. (Previously presented) The method of claim 1 wherein the compound capable of stimulating an endogenous immune response comprises at least one NK cell or T cell stimulant.

27. (Previously presented) The method of claim 1 wherein the conjugate composition is administered in multiple injections.

28. (Original) The method of claim 1 wherein the host animal had been previously exposed naturally to the immunogen so that the host animal has a preexisting immunity to said immunogen evidenced by the presence of endogenous antibodies to the immunogen.

29. (Original) The method of claim 1 wherein the host animal had been previously exposed to the immunogen by a non-natural process resulting in priming of the host animal's immune response to said immunogen.

30. (Previously presented) The method of claim 29 wherein the non-natural process resulting in priming of the animal's immune response is vaccination.

31. (Previously presented) The method of claim 29 wherein the non-natural process resulting in priming of the immune response is active immunization.

32. (Original) The method of claim 1 wherein the endogenous immune response comprises a humoral immune response.

33. (Previously presented) The method of claim 32 wherein the humoral response is an acquired immune response.

34. (Previously presented) The method of claim 32 wherein the humoral response is an innate immune response.

35. (Previously presented) The method of claim 33 wherein the acquired response is induced by administering into the host animal a vaccine composition.

36. (Original) The method of claim 1 wherein the endogenous immune response comprises a cell-mediated immune response.

37. (Original) The method of claim 1 wherein the endogenous immune response comprises a humoral and a cell-mediated immune response.

38. (Previously presented) A method of enhancing an endogenous immune response-mediated specific elimination of a population of cancer cells in a host animal harboring said population wherein said population expresses a binding site for a folate receptor-binding ligand, said method comprising the steps of

administering to the host a composition comprising a conjugate of said ligand and an immunogen;

administering to the host antibodies directed against the immunogen; and

administering to said host a stimulant of an endogenous immune response that does not bind to the ligand-immunogen conjugate.

39. (Canceled)

40. (Canceled)

41. (Previously presented) A method of enhancing an endogenous immune response-mediated specific elimination of a population of cancer cells in a host

animal harboring said population wherein said population preferentially expresses, uniquely expresses, or overexpresses a folic acid receptor, said method comprising the steps of

administering to said host a composition comprising a covalently linked conjugate of a ligand and an immunogen wherein the immunogen is recognized by an endogenous or exogenous antibody in the host or is recognized directly by an immune cell in the host;

wherein the ligand comprises folic acid or a folic acid analog having a glutamyl group wherein the covalent linkage is only through the γ- carboxy group of the glutamyl group; and

administering to said host a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.

42. (Previously presented) A method of enhancing an endogenous immune response-mediated specific elimination of a population of cancer cells in a host animal harboring said population wherein said population preferentially expresses, uniquely expresses, or overexpresses a folic acid receptor, said method comprising the step of

administering to said host a composition comprising a covalently linked conjugate of a ligand and an immunogen wherein the immunogen is recognized by an endogenous or exogenous antibody in the host or is recognized directly by an immune cell in the host;

wherein the ligand comprises folic acid or a folic acid analog having a glutamyl group wherein the covalent linkage is only through the α- carboxy group of the glutamyl group; and

administering to said host a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.

43. (Previously presented) A pharmaceutical composition comprising therapeutically effective amounts of an immunogen conjugated to a folate receptor-binding

ligand selected from the group consisting of folate and analogs thereof, a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate, and a pharmaceutically acceptable carrier therefor.

44. (Previously presented) The pharmaceutical composition of claim 43 in a parenteral prolonged release dosage form.

45. (Previously presented) The pharmaceutical composition of claim 43 wherein the compound capable of stimulating an endogenous immune response is a cytokine.

46. (Previously presented) The pharmaceutical composition of claim 45 wherein the cytokine comprises a compound selected from the group consisting of IL-2, IL-12, IL-15, IFN-α, IFN-γ, and GM-CSF, or combinations thereof.

47. (Withdrawn) A method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein the members of said cell population have an accessible binding site for a ligand, said method comprising the step of

administering to said host a composition comprising an immunogen conjugated to the ligand wherein said immunogen is recognized by an endogenous or an exogenous antibody in the host or is recognized directly by an immune cell in the host; and

administering to said host a therapeutic factor, said factor being selected from the group consisting of a cell killing agent, a tumor penetration enhancer, a chemotherapeutic agent, an antimicrobial agent, a cytotoxic immune cell, and a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.

48. (Cancelled)

49. (Cancelled)

50. (Previously presented) The pharmaceutical composition of claim 43 wherein the immunogen is a hapten.

51. (Previously presented) The pharmaceutical composition of claim 50 wherein the hapten is fluorescein or dinitrophenyl.

52. (Cancelled)

53. (Previously presented) The method of claim 8 wherein the bonding is covalent bonding through a divalent linker.

54. (Previously presented) The method of claim 8 wherein the bonding is direct covalent bonding.